Leptin and its role in pregnancy and fetal development – an overview

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Abstract

Leptin is a hormone that is secreted by adipose cells in proportion to adipose mass, and therefore a low leptin level signifies depletion of energy stores. It has been proposed that leptin is one of the signals controlling sexual maturation. For example, humans and rodents lacking leptin fail to undergo complete puberty, while overexpression of leptin in mice causes early puberty. The placenta also produces leptin in human pregnancy, increasing the amount in the maternal circulation. The effects of the increased leptin levels during pregnancy are not clear. In contrast, the mouse placenta does not produce endocrinologically significant amounts of leptin. The mouse placenta does secrete a leptin-binding protein, the production of which correlates with a large increase in maternal leptin levels. The physiology of leptin during pregnancy and fetal development differs significantly between species, and is not well understood in any.

Introduction to leptin biology

Leptin is a hormone that is produced predominantly by adipose cells [1,2]. Circulating leptin levels are proportional to adipose tissue mass. Thus leptin levels can be thought of as a signal to the body of its energy reserves. Although often discussed in terms of elevated leptin levels in...
obesity, it is more likely that the physiological importance of leptin is that low levels signal starvation [3]. Indeed, many of the adaptive responses to fasting can be ameliorated by leptin infusion. Most of our knowledge about leptin has come from studying rodents with genetic leptin deficiency (ob/ob mice), or leptin receptor mutations (db/db mice, fa/fa rats). There are also a handful of human patients with mutations in these genes.

Determination of the sites of leptin action is confounded by the fact that there are multiple leptin receptor mRNA splicing isoforms, with different cytoplasmic tails. The leptin receptor (including all mRNA isoforms) is expressed in many tissues. However, expression of the OB-Rb long form, which is competent for signalling via the JAK/STAT (Janus kinase/signal transduction and activators of transcription) pathway, is usually much lower than expression of the OB-Ra short form, which cannot signal via this pathway. Disruption of long-form signalling is sufficient to cause the complete leptin-deficient phenotype. However, certain kinds of signalling may occur via the short form.

The central nervous system is where leptin exerts the bulk of its effects on energy metabolism. Leptin decreases food intake, increases energy expenditure and decreases metabolic efficiency. The arcuate nucleus of the hypothalamus has leptin receptors that stimulate downstream neurons upon activation by leptin. Long-form leptin receptors are also found in other hypothalamic neurons.

It is important to note that a number of tissues besides adipose tissue (and placenta, discussed below) can produce leptin, at least under certain circumstances. These include mammary epithelium [4], gastric fundus [5] and muscle [6]. The amount of leptin produced tends to be small, and thus these sources of leptin are probably more important for paracrine or autocrine pathways, rather than for endocrine regulation of energy expenditure. Leptin also has effects in addition to those on energy homoeostasis (for example, on bone) that are mediated via the central nervous system [7], and other actions (on haematopoiesis [8] and angiogenesis [9]) that probably occur via direct leptin binding to peripheral target cells.

Leptin is required for sexual maturity

In addition to obesity and insulin resistance, the phenotype of mice lacking leptin includes incomplete sexual maturity. A human patient lacking leptin also showed delayed puberty [10]. Gonadotropin levels in ob/ob mice are low [11], and infertility in female ob/ob mice can be partially overcome by gonadotropin injections [12]. Leptin injections also lead to completion of genitalia development in female and male ob/ob mice [13–15]. This is a very sensitive effect of leptin, requiring only low doses [16], consistent with the teleological idea that only extreme starvation should prevent maturation, since that animal can no longer contribute to the gene pool. Leptin’s effects on sexual maturity almost certainly occur via receptors on hypothalamic neurons that synapse directly or indirectly with hypothalamic gonadotropin-releasing hormone neurons [17]. The gonadotropin-releasing hormone released causes pituitary secretion of follicle-stimulating hormone and luteinizing hormone.

A certain level of ‘fatness’ has been proposed as a requirement for entry into puberty [18]. The discovery of leptin provided a candidate molecule to mediate this signal. In addition to the incomplete sexual maturity in the setting of leptin deficiency, noted above, increasing the leptin levels in normal mice causes earlier puberty (e.g. vaginal opening, fertility, increased reproductive organ weight) [19,20]. There are conflicting data about whether changes in leptin levels are correlated with puberty in humans [21,22] and rhesus monkeys [23]. In summary, leptin is one of the signals that regulate entry into, and completion of, maturation of the reproductive system, although it is unlikely to be the sole signal.

Leptin in mouse pregnancy

Leptin biology during pregnancy varies markedly by species. In mice, maternal circulating leptin levels rise ~20–40-fold by term [14,24]. Concomitant with this rise is an increase in the level of a soluble form of the leptin receptor, encoded by the OB-Re isoform and produced by the placenta [14]. OB-Re transcription uses a novel start site [55 bases upstream of the first ATG, at base 458 (GenBank U52915)] and a subset of mRNAs includes an insertion of 'T'T'T'TTGTCTC-TGCCCAGGTCTTGCTTCAGCGCCACGGGAGCCCTAGGGGA-ACTGTCAG between bases 21 and 20 upstream of the first ATG (O. Gavrilova and M. L. Reitman, unpublished work). The OB-Re protein binds leptin with high affinity. The increase in leptin-binding activity accounts quantitatively for the increase in circulating leptin, possibly by
preventing leptin clearance by the kidney. It is not known whether the bound leptin is available for signalling via leptin receptors.

Two lines of evidence suggest that maternal adipose tissue, and not the placenta, produces the circulating leptin. First, leptin was not detectable in the placenta by Northern blot analysis (with a detection limit of 1/1000 the level in adipose tissue) [14,24]. To confirm a maternal source, ob/ob females were bred with wild-type (+/+ ) males. Despite the fact that the resulting placentaland fetal tissues are +/+ (and thus have one intact leptin allele), no leptin was detected in the maternal circulation [14]. It follows that maternal adipose tissue, and not the fetus/placenta, is the only significant source of circulating leptin in the mother.

Interestingly, Hoggard et al. [25,26], using reverse transcription-PCR or in situ hybridization, were able to detect leptin expression in the placenta. Presumably the increased sensitivity of their assays explains the different conclusion. These studies also detected leptin mRNA in multiple other fetal tissues, including cartilage/bone, heart, liver and hair follicles [25,26].

**Leptin in rat pregnancy**

Maternal circulating leptin levels increase by 1.2-2-fold during pregnancy in rats [27,28]. The increase is correlated with the increase in fat mass [29]. However, there is also no large increase in binding proteins, and there are low levels of placental leptin mRNA [27,28,30-32]. Just before parturition and during lactation, leptin levels are slightly reduced, presumably reflecting adipose triacylglycerol stores [27,28,30].

**Leptin in human pregnancy**

In humans, the placenta is a significant source of maternal circulating leptin, with levels in the second and third trimesters being 150-200% of those in the first trimester or in the non-gravid situation [33,34]. In patients with trophoblastic neoplasms (hydatidiform mole or choriocarcinomas), leptin levels are greatly increased; these are reduced after treatment of the tumours [33]. Perfusion studies in dually perfused isolated placental cotyledons demonstrated that 98.6% of the leptin secreted went to the maternal side [35]. Thus maternal leptin levels are the sum of leptin secretion from adipose tissue, which is proportional to maternal fat levels, and from the placenta, which occurs at an adiposity-independent rate. This explains why maternal leptin levels do not correlate well with body mass index (BMI) at low BMI values, but do show a correlation with higher BMIs.

Leptin is produced in the syncytiotrophoblasts and the amnion cells of the human placenta. Placental transcription of leptin uses the same promoter as in adipose cells. A plausible explanation for the increased placental transcription is an upstream enhancer that is active in choriocarcinomas cells but inactive in adipose cells [36]. Interestingly, the enhancer is located within a MER11 repetitive element. It is possible that insertion of this element is the evolutionary event that significantly increased placental leptin transcription. The observation that the insertion is present in all primates examined (human, chimp, gorilla, bonobo and orang utan; B. Marcus-Samuels, A. Varki and M. L. Reitman, unpublished work) suggests that these primates may also have significant placental expression of leptin.

Cord blood leptin levels are generally correlated with fetal weight (e.g. [37,38]), but show a better correlation with neonatal fat mass [39]. Higher leptin levels in arterial than in venous blood constitute further evidence that cord blood levels reflect fetal leptin production ([37], but see [40]). Presumably the leptin is being produced by adipose tissue, but it is possible that other fetal tissues contribute. Fetuses of mothers with gestational diabetes mellitus have higher leptin levels, which are correlated with abdominal fat content [40].

**Role of leptin in pregnancy: maternal leptin and energy homoeostasis**

Understanding the function of increased maternal leptin levels during pregnancy is a daunting task. One can speculate at length, but finding proof is difficult. Why does the human placenta make leptin and secrete it systemically? A priori, one might have expected that a low maternal leptin level would be desirable during gestation, since the metabolic effects of high leptin levels (metabolic inefficiency and decreased food intake) are undesirable, and indeed are not observed, when the mother is putting great nutritional effort into the fetus and preparation for lactation. One can postulate that, during gestation, leptin has novel endocrine functions, distinct from those in the non-gravid state. If a low leptin concentration signals starvation, then the placenta-derived leptin could act as a safety valve, preventing leptin levels from reaching ‘too low’ a level. But what exactly is this protecting from? Regarding the metabolic
effects of leptin, it appears that human pregnancy, like obesity (another condition characterized by high leptin levels), is a leptin-resistant state. Thus the hyperleptinaemia could be a compensatory response.

Another possibility is that the placental leptin might have a paracrine role in maintaining pregnancy or in preparation for parturition. A more nihilistic possibility is that the increase in leptin production during human pregnancy is merely the result of a random evolutionary event and is without functional significance. In this scenario, any detrimental effects of a high leptin level must not be disadvantageous enough to have precluded survival during recent evolution.

Since the endocrinology of pregnancy in general, and leptin in particular, are not well conserved between species, the functions of leptin during pregnancy may differ between species. In the mouse, the elevated total leptin levels may be misleading. If bound leptin is inactive and free leptin is actually reduced in amount, then there is in fact less leptin available for signalling. This scenario would be consistent with the expectation that the effects of leptin would not be desirable during pregnancy.

About the only relevant data on the functions of leptin during gestation come from experiments in which ob/ob male and female mice were treated with leptin to allow them to become fertile, and then leptin was withdrawn from the mother. These completely leptin-deficient mothers carried to term and delivered normal-appearing leptin-deficient pups [41]. This strongly suggests that (in mice) leptin is not essential for a complete gestation.

Role of leptin in pregnancy: fetal leptin and development

As noted above, leptin mRNA has been detected in multiple mouse fetal tissues. This observation is intriguing. However, it is not clear which tissues produce sufficient to have an endocrine effect in the fetus, and which tissues produce levels that are likely to have only local effects. It is notable that mice and rats with mutated leptin or leptin receptor genes are not distinguishable from wild-type littersmates until about 2 weeks after birth. Thus it appears that fetal leptin production is either not essential or is compensated by the maternal hormone or by other maternal or fetal factors.

Conclusions

The biology of leptin during pregnancy is surprisingly divergent in mice, rats and humans. Mice produce high levels of a binding protein, while humans and rats do not. Humans synthesize leptin in the placenta at significant levels, while mice do not. The role of increased circulating maternal leptin is unclear. It seems plausible that placental leptin production could have a paracrine or autocrine function. Fetal leptin appears to be produced in adipose tissue and multiple other tissues. Again, the function(s) of this hormone may be paracrine, but this remains to be proven.

References

Regional differences in protein production by human adipose tissue

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Abstract

Human adipose tissue has an important protein secretory function. Cytokines, hormones, pro-hormones and enzymes are secreted from fat cells and act in an endocrine or paracrine fashion. The production of several of these proteins is affected by obesity; normally there is an increase in the obese state. Protein production is, as a metabolic activity, subject to regional variations. In particular, the production of leptin, angiotensinogen, interleukin-6 and plasmin activator inhibitor-1 differs between subcutaneous and visceral adipose tissue sites, but no regional differences have been reported in the production of tumour necrosis factor α. It is possible that regional variations in protein production by adipose tissue are of importance in some of the endocrine and metabolic disturbances seen in various forms of obesity, such as visceral and upper-body obesity.

Introduction

It is well known that human adipose tissue is a heterogeneous metabolic organ [1]. Increased release of fatty acids from visceral fat has important effects on the liver and can explain many metabolic abnormalities in subjects with upper-body obesity [1]. An important secretory function of adipose tissue has been demonstrated recently; fat cells produce and secrete a number of cytokines, pro-hormones, hormones and enzymes, which act in a paracrine or endocrine fashion [2]. The production of most (but not all) of these proteins is increased in the adipose tissue of obese subjects, and it is possible that increased endocrine/